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The Use of Digoxin in Patients With Worsening Chronic Heart Failure



Reconsidering an Old Drug to Reduce Hospital Admissions

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Digoxin is the oldest cardiac drug still in contemporary use, yet its role in the management of patients with heart failure (HF) remains controversial. A purified cardiac glycoside derived from the foxglove plant, digoxin increases ejection fraction, augments cardiac output, and reduces pulmonary capillary wedge pressure without causing deleterious increases in heart rate or decreases in blood pressure. Moreover, it is also a neurohormonal modulator at low doses. In the pivotal DIG (Digitalis Investigation Group) trial, digoxin therapy was shown to reduce all-cause and HF-specific hospitalizations but had no effect on survival. With the discovery of neurohormonal blockers capable of reducing mortality in HF with reduced ejection fraction, the results of the DIG trial were viewed as neutral, and the use of digoxin declined precipitously. Although modern drug and device-based therapies have dramatically improved the survival of ambulatory patients with HF, outcomes for patients with worsening chronic HF, defined as deteriorating signs and symptoms on standard therapy often leading to unscheduled clinic or emergency department visits or hospitalization, have largely remained unchanged over the past 2 decades. The available data suggest that a therapeutic trial of digoxin may be appropriate in patients with worsening chronic heart failure who remain symptomatic. (J Am Coll Cardiol 2014;63:1823–32) © 2014 by the American College of Cardiology Foundation

*After all, in spite of opinion, prejudice, or error,
time will fix the real value upon this discovery.*

—Sir William Withering,
Birmingham, United Kingdom, July 1, 1785 (1)

*It was decided to proceed with the proposal for digitalization....
There was no dyspnea on lying flat....
The lungs were entirely clear.*

—Dr. Howard G. Bruenn on treating
President Franklin D. Roosevelt (2)

Digoxin, a purified cardiac glycoside derived from the foxglove plant, is the oldest cardiac drug still in contemporary use (1). At its peak, digoxin was prescribed to an estimated 80% of patients with heart failure (HF) in the

United States (3–5). However, in the context of the pivotal beta-blocker and angiotensin-converting enzyme inhibitor trials, the results of the DIG (Digitalis Investigation Group) trial (6), which showed that digoxin reduces the risk for hospitalization but not mortality, were interpreted with disappointment, and its use subsequently declined (Table 1) (7–13). As a result, although digoxin received approval from the U.S. Food and Drug Administration in 1997, the major guideline-issuing professional societies currently offer a secondary recommendation for digoxin in patients with HF with reduced ejection fraction (EF) in normal sinus rhythm experiencing persistent symptoms despite optimal medical therapy (14–16).

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Abbreviations and Acronyms

CI = confidence interval
CV = cardiovascular
EF = ejection fraction
HF = heart failure
HR = heart rate
NYHA = New York Heart Association
RR = risk ratio
SDC = serum digoxin concentration

Although the management of ambulatory patients with HF with reduced EF has been revolutionized over the past couple of decades by drug and device-based therapies with a mortality benefit (17), patients with worsening chronic HF, defined as deteriorating signs and symptoms on standard therapy often leading to unscheduled clinic or emergency department visits or hospitalizations, remain at high risk for admission or death (18,19). To

confront this growing challenge, the Centers for Medicare and Medicaid Services have implemented financial disincentive for hospitals with excessive 30-day readmissions for HF. Given this financial impetus, it is an opportune time to reconsider existing therapies capable of reducing HF-related hospitalizations and readmissions (18,20). Thus, in this review we seek to critically reevaluate the available data on the role of digoxin in the contemporary management of HF and to provide a conceptual framework for future research.

Mechanism of Action

Digoxin and other cardiac glycosides function by inhibiting the membrane-bound Na^+/K^+ -adenosine triphosphatase, thereby impeding the transport of sodium from the intracellular to the extracellular space (21). The resulting loss of the transmembrane sodium gradient decreases the activity of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger, disrupting Ca^{2+} homeostasis and increasing intracellular levels. In myocytes, raising the intracellular Ca^{2+} concentration, the pivotal link in excitation-contraction coupling, increases inotropy and the force generated (22–24). As a result, in patients with systolic dysfunction, digoxin improves left ventricular EF, augments cardiac output, and reduces pulmonary capillary wedge pressure without causing deleterious increases in heart rate (HR) or decreases in blood pressure (Table 2) (25–28).

Table 1

Prevalence of Digoxin Use at Admission and Discharge in Representative Hospital-Based Registries of Patients Admitted With Primary Diagnoses of HF

Registry	Admission	Discharge
ADHERE	30/19	44/21
OPTIMIZE-HF	30/17	38/19
EFHS II	27	31
EFICA	19	17
RO-AHFS	35	40
IN-HF Outcome	16	~24
ATTEND	~15	~25

Reported as overall percentages or divided into reduced/preserved EF.

ADHERE = Acute Decompensated Heart Failure National Registry; ATTEND = Acute Decompensated Heart Failure Syndromes; EF = ejection fraction; EFHS = EuroHeart Failure Survey; EFICA = Etude Française de l'Insuffisance Cardiaque Aiguë; HF = heart failure; IN-HF = Italian Registry on Heart Failure; OPTIMIZE-HF = Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure; RO-AHFS = Romanian Acute Heart Failure Syndromes.

For many years, it was thought that digoxin exerted its effects primarily in the myocardium, but it is now recognized that the physiologic properties of digoxin are a result of inhibition of Na^+/K^+ -adenosine triphosphatase in cardiac and noncardiac tissues alike (29). In noncardiac tissue, digoxin acts as a neurohormonal modulator by increasing parasympathetic tone and decreasing activation of the sympathetic nervous system and renin-angiotensin-aldosterone system (27,30–32). Furthermore, in addition to its direct sympatholytic effects at low doses, digoxin indirectly decreases sympathetic outflow by improving carotid sinus baroreceptor sensitivity. Although digoxin improves the overall neurohormonal profile in patients with severe HF at low doses, it should be noted that further dose increases within the therapeutic range have no added neurohormonal benefit and may in fact be sympathomimetic (33,34).

Finally, digoxin slows firing at the sinoatrial node and prolongs conduction at the atrioventricular node but has limited electrophysiological effects on the remainder of the conduction system. Thus, digoxin has minimal proarrhythmic effects when dosed to achieve guideline-recommended serum digoxin concentrations (SDCs) (14–16). In contrast, at supratherapeutic SDCs or therapeutic SDCs with concomitant hypokalemia, atrioventricular block and escape rhythms are the most common electrocardiographic manifestations of toxicity.

Digoxin Withdrawal Trials

Before the pivotal DIG trial, numerous small to medium-sized randomized, double-blind, placebo-controlled trials provided evidence that digoxin improves hemodynamics and clinical status in ambulatory patients with HF with reduced EF receiving background therapy including diuretic agents with or without oral vasodilators (35). The most compelling evidence was derived from PROVED (Prospective Randomized Study of Ventricular Function and Efficacy of Digoxin) (36) and RADIANCE (Randomized Assessment of Digoxin on Inhibitors of the Angiotensin Converting Enzyme) (37) trials, which tested the hypothesis that digoxin withdrawal from background therapy would lead to clinical deterioration. Both studies enrolled stable ambulatory patients with HF with EFs $\leq 35\%$ and New York Heart Association (NYHA) functional class II or III symptoms in normal sinus rhythm and randomized them

Table 2 Physiologic Effects of Digoxin Therapy

Hemodynamic	Neurohormonal	Electrophysiological
↑ LVEF	↑ Parasympathetic	SA node: slows sinus rate
↑ CO	↓ Sympathetic	AV node: prolongs conduction
↓ HR, ↔ BP	↓ RAAS	
↓ PCWP		

Modified and reprinted, with permission, from Gheorghiade et al. (4).

AV = atrioventricular; BP = blood pressure; CO = cardiac output; HR = heart rate; LVEF = left ventricular ejection fraction; PCWP = pulmonary capillary wedge pressure; RAAS = renin-angiotensin-aldosterone system; SA = sinoatrial.

to either continue digoxin therapy or switch to placebo in addition to background therapy for 12 weeks. In the PROVED and RADIANCE protocols, the investigators were encouraged to optimize background HF therapy, which, respectively, included diuretic agents and diuretic agents plus angiotensin-converting enzyme inhibitors.

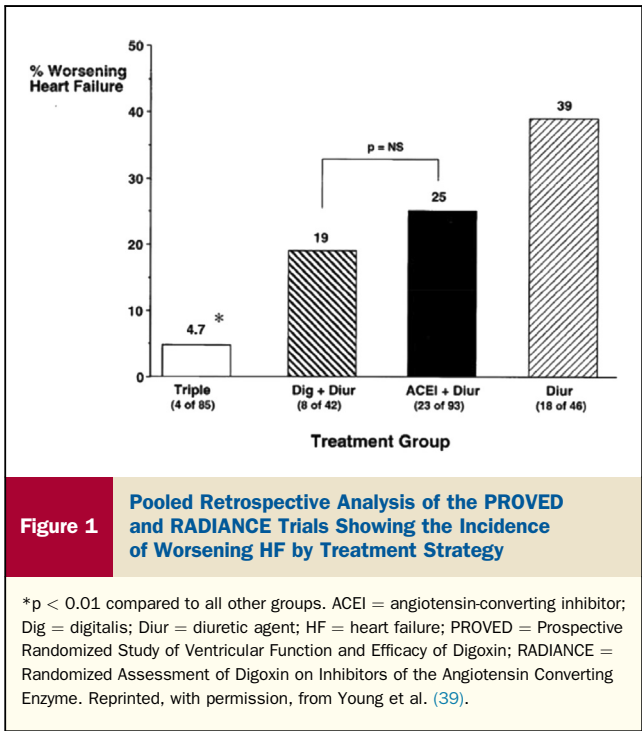
In both trials, digoxin continuation led to a lower incidence of treatment failure (defined as subjective and objective evidence of worsening HF severe enough to require a therapeutic intervention), improved exercise tolerance, and increased left ventricular EF (Table 3). Among patients receiving diuretic agents and angiotensin-converting enzyme inhibitors, continuation of digoxin also led to fewer signs and symptoms of volume overload and better quality-of-life scores. However, the relative clinical efficacy of digoxin may be overstated in these studies because digoxin was removed from a previously stable medication regimen. In contrast, a substudy of the DIG trial examining health-related quality of life found that digoxin improved only perceived health at 4 months but had no discernible effect on any of the domains assessed at 12 months (38). Finally, pooled retrospective analyses of the PROVED and RADIANCE trials suggested that triple therapy with digoxin in addition to an angiotensin-converting enzyme inhibitor and a diuretic agent was associated with the lowest incidence of worsening HF and found that digoxin therapy reduced overall health care expenditures, setting the stage for the pivotal DIG trial (Fig. 1) (39,40).

The DIG Trial

The DIG main trial was self-described as a “simple” phase III trial cosponsored by the National Heart, Lung, and

Table 3 Effects of Digoxin in Stable Ambulatory Patients With HF in Normal Sinus Rhythm With Reduced EF Receiving Diuretic Agents (PROVED) or Diuretic Agents and ACE Inhibitors (RADIANCE)		
End Point	On Diuretic Agents	On ACE Inhibitors and Diuretic Agents
Treadmill time	Improved	Improved
6-min walk distance	No change	Improved
Incidence of treatment failure	Decreased	Decreased
Time to treatment failure	Decreased	Decreased
Change in signs and symptoms of heart failure	No change	Improved
Quality of life (Minnesota Living With Heart Failure Questionnaire)	No change	Improved
CHF score	No change	Improved
Global evaluation of progress	No change	Improved
LVEF	Improved	Improved
HR and BP	Decreased	Decreased
Body weight	Decreased	Decreased

Modified and reprinted, with permission, from Eichhorn et al. (35).
ACE = angiotensin-converting enzyme; CHF = congestive heart failure; EF = ejection fraction; PROVED = Prospective Randomized Study of Ventricular Function and Efficacy of Digoxin; RADIANCE = Randomized Assessment of Digoxin on Inhibitors of the Angiotensin Converting Enzyme; other abbreviations as in Table 2.



Blood Institute and the U.S. Department of Veterans Affairs Cooperative Studies Program, designed to study the effects of digoxin on mortality and hospitalization in 6,800 stable ambulatory patients with HF with EFs ≤45% in normal sinus rhythm, irrespective of digoxin treatment status at enrollment (6,41). Patients were randomized in a double-blind fashion to receive digoxin or placebo once daily in addition to background therapy. The recommended initial daily dose was determined using an algorithm incorporating age, sex, weight, and renal function, but final dosing was left to the discretion of the site investigator. Patients treated with digoxin before enrollment were randomized without a preceding washout period. Follow-up visits were scheduled for weeks 4 and 16 and every 4 months thereafter, for a mean duration of 37 months (range: 28 to 58 months).

Study participants had a mean age of 65 years, were predominantly white men, and reported NYHA functional class II or III symptoms (Table 4). Nearly one-half of the patients were receiving digoxin at the time of enrollment, and there was high background use of angiotensin-converting enzyme inhibitors (about 95%) and diuretic agents (about 80%). More than 80% of digoxin-treated patients received daily doses of study drug ≥0.250 mg. Although all-cause mortality did not differ between the digoxin and placebo arms (Fig. 2A), there was a trend toward a lower risk for HF-specific mortality (394 vs. 449 deaths; risk ratio [RR]: 0.88; 95% confidence interval [CI]: 0.77 to 1.01; p = 0.06). In contrast, the incidence of all-cause, cardiovascular (CV)-related, and HF-related hospitalization was significantly lower in patients randomized to digoxin (Table 4). In addition, the incidence of death or hospitalization for worsening HF (Fig. 2B), although not a

Table 4 Baseline Clinical Characteristics and Outcomes by Treatment Assignment in the DIG Trial

Clinical Characteristic/ Outcome	Digoxin	Placebo	p Value
Age, yrs	63.4 ± 11.0	63.5 ± 10.8	
Women	22.2%	22.5%	
Nonwhite race	14.4%	14.8%	
NYHA functional class			
I	13.7%	13%	
II	55.3%	54.5%	
III	30.7%	30.5%	
IV	2.2%	1.9%	
Prior digoxin	44.1%	44.6%	
Concomitant therapies			
Diuretic agents	81.2%	82.2%	
ACE inhibitors	94.1%	94.8%	
Nitrates	42.1%	43.1%	
Daily dose of study drug, mg			
0.125	17.5%	17.4%	
0.250	70.6%	70%	
0.375	10.3%	11.3%	
0.500	1.1%	0.9%	
Cause of death			
All	34.8%	35.1%	0.80
CV	29.9%	29.5%	0.78
Worsening HF	11.6%	13.2%	0.06
Other CV	15.0%	13.0%	—
Reason for hospitalization			
All	64.3%	67.1%	0.006
CV	49.9%	54.4%	<0.001
Worsening HF	26.8%	34.7%	<0.001
Other CV	23.1%	19.7%	—
Non-CV/unspecified	40.7%	39.6%	—

Values are mean ± SD or %.

ACEI = angiotensin-converting enzyme; CV = cardiovascular; DIG = Digitalis Investigation Group; HF = heart failure; NYHA = New York Heart Association.

pre-specified outcome, was significantly lower in the digoxin group (1,041 vs. 1,291 patients; RR: 0.75; 95% CI: 0.69 to 0.82; $p < 0.001$). Finally, the incidence of hospitalization for suspected digoxin toxicity was 2-fold higher in digoxin-treated patients but still relatively low overall (67 vs. 31 events; RR: 2.17; 95% CI: 1.42 to 3.32; $p < 0.001$).

The DIG ancillary trial had a similar design and was conducted in parallel to the main study but included patients with EFs $>45\%$ (42). The ancillary trial enrolled a total of 988 patients and found no effects on all-cause, CV-specific, or HF-specific mortality or on all-cause or CV hospitalizations. However, there was a trend toward a reduction in hospitalization for worsening HF (108 vs. 89 events; RR: 0.79; 95% CI: 0.59 to 1.04; $p = 0.094$), which was offset by a trend toward an increase in hospitalization for unstable angina (62 vs. 82 events; RR: 1.37; 95% CI: 0.99 to 1.91; $p = 0.061$).

Although straightforward in its design, there are a number of details concerning the DIG trial meriting further mention. First, the study population was about 5 to 10 years younger than an unselected population of ambulatory patients with HF (43) and included few women (about 20%)

and racial minorities ($<15\%$), limiting its generalizability. Second, digoxin was stopped in about 50% of the patients randomized to placebo, without a washout period, and $>20\%$ of patients in the placebo group received open-label digoxin at some point during follow-up, which, respectively, would tend to bias the data to reject and accept the null hypothesis. In addition, digoxin levels were considered therapeutic if the SDC was between 0.5 and 2.0 ng/ml, while current guidelines (14,15,44) recommend an SDC between 0.5 and 0.9 ng/ml. As a result, it is notable that the mean SDC was 0.86 ng/ml at the 1-month visit and 0.80 ng/ml at the 12-month visit, suggesting that nearly one-half of the patients enrolled in the DIG trial had supra-therapeutic SDCs by modern standards, yet digoxin therapy did not adversely affect survival.

Finally, although digoxin has been part of background therapy for most pivotal clinical trials, many modern medical (i.e., β -blockers and mineralocorticoid receptor antagonists) and device (i.e., implantable cardioverter-defibrillators and/or cardiac resynchronization therapy) therapies were not yet a part of background therapy when the DIG trial was conducted, potentially limiting the applicability of these data to contemporary clinical practice. Thus, the aforementioned considerations and the differential benefit of digoxin on HF-specific morbidity and mortality have made the DIG trial database an active area of investigation since its initial publication.

Retrospective Analyses of Digoxin Trials

The revised recommendation suggesting a therapeutic SDC of 0.5 to 0.9 ng/ml instead of 0.5 to 2.0 ng/ml (14,15,44) is based on several post-hoc analyses of the DIG trial and other clinical trial databases suggesting that it may be possible to obtain the favorable effects of digoxin with an SDC <1.0 ng/ml (33,34,45–47). Before the DIG trial, it had been shown that the hemodynamic and neurohormonal effects of digoxin occur at low digoxin doses and that increasing the dose does not always results in additional benefit (33,34,46). Similarly, pooled analysis of the PROVED and RADIANCE studies found that the effects of digoxin were comparable at lower (<1.0 ng/ml) and higher SDCs.

After completion of the DIG trial, a comprehensive post-hoc analysis including all patients enrolled in the main and ancillary trials with properly measured SDCs (about 80% of study participants) was performed to assess the interaction between SDC and long-term morbidity and mortality (45). This study found that HF hospitalizations were reduced in the digoxin arm compared with placebo irrespective of SDC, while survival was improved only in those patients randomized to digoxin with SDCs ≤ 0.9 ng/ml (Fig. 3). Of note, the survival benefit was robust and consistent across age, sex, EF, and comorbid disease states.

There has also been substantial interest in the sex-specific effects of digoxin, because women made up only about 20%

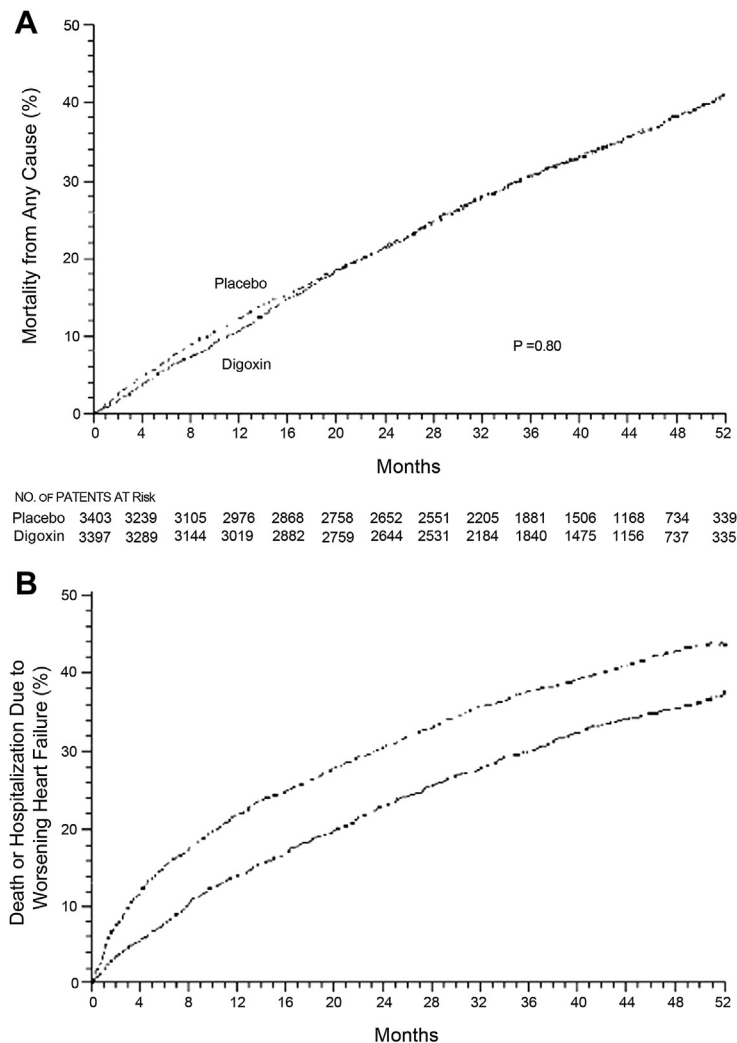


Figure 2 All-Cause Mortality and Incidence of Death or Hospitalization for Worsening HF in the DIG Trial

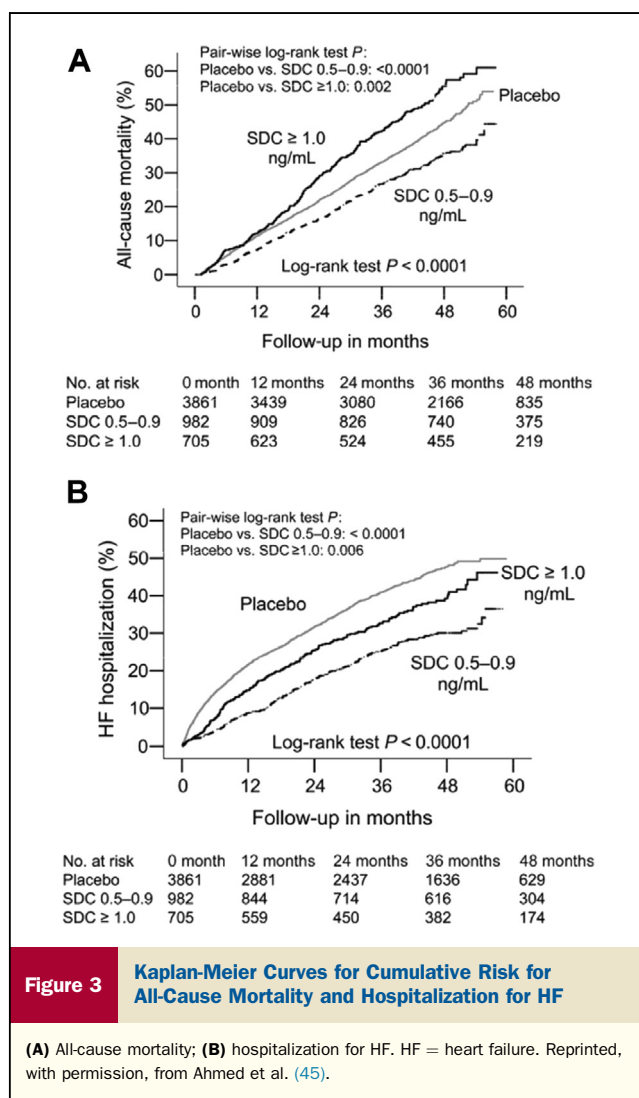
(A) All-cause mortality; (B) incidence of death or hospitalization due to worsening HF. Reprinted, with permission, from the Digitalis Investigation Group (6). DIG = Digitalis Investigation Group; HF = heart failure.

of total enrollment in the DIG trial. Although initially it had been suggested that all-cause mortality may have been increased in women randomized to digoxin (48), subsequent analysis of the DIG main trial taking into account SDC found only women with SDCs >1.0 ng/ml to be at higher risk for mortality (49). Furthermore, compared with placebo, there was a significant inverse relationship between the risk for all-cause mortality and SDC in both men and women (Fig. 4). Although in women, the point estimates for the risk for mortality for SDC <1.0 ng/ml did not reach the threshold for statistical significance, many fewer women were enrolled in the DIG trial, decreasing statistical power to detect a difference.

In addition, several retrospective investigations of the DIG trial database have found digoxin to have beneficial effects in high-risk groups regardless of SDC. First, a

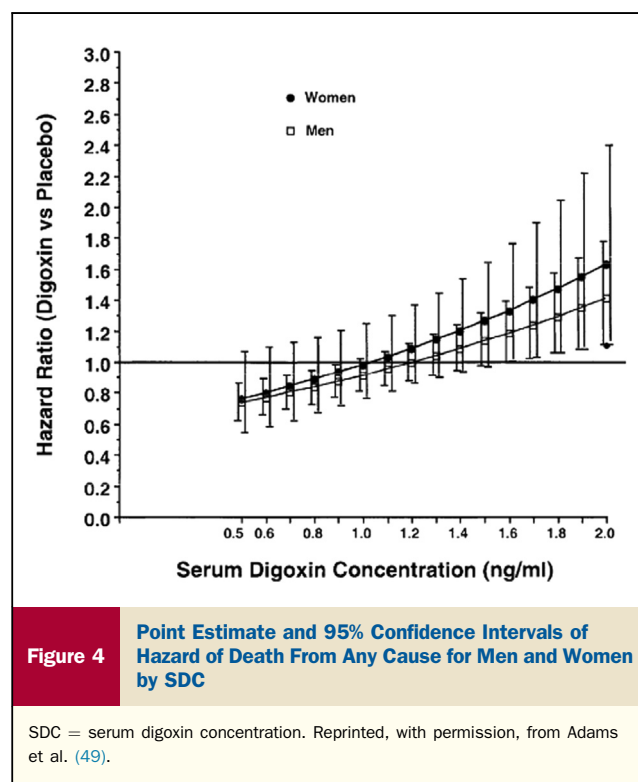
pre-specified subgroup analysis of the DIG trial found that patients with NYHA functional class III or IV symptoms, left ventricular EFs <25%, and cardiothoracic ratios >55% treated with digoxin had improvements in 2-year outcomes, including HF-specific death or hospitalization, all-cause hospitalization, and all-cause mortality (Fig. 5) (50). Similarly, another study found that digoxin reduces 30-day all-cause hospitalizations in ambulatory patients with HF ≥65 years of age, establishing a short-term clinical benefit in elderly patients (Fig. 6) (51).

Finally, patients randomized to digoxin more commonly experienced improvements in renal function (defined as a ≥20% increase in estimated glomerular filtration rate), a clinical finding that was associated with a reduction in the composite of mortality and hospitalization (52,53). This finding is clinically relevant, as cardiorenal interactions



are known to contribute to the pathophysiologic progression of HF, and renal function often limits the initiation and titration of evidence-based medications (i.e., angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and mineralocorticoid receptor antagonists) as well as diuretic therapy. Further research is required to validate the hypothesis that the long-term beneficial effects of digoxin are mediated by the preservation or frank recovery of renal function.

The DIG database was recently reanalyzed to look at the primary composite end point used in the SHIFT (Systolic Heart Failure Treatment With the I_f Inhibitor Ivabradine Trial) to compare the effect of digoxin with that of this novel agent (54). Treatment with digoxin and ivabradine resulted in relative risk reductions in CV death or hospital admission for worsening HF, respectively, of 15% (95% CI: 9% to 21%) and 18% (95% CI: 10% to 25%). There is a growing recognition that an elevated HR may portend a poor prognosis and be a potential target for therapy (55). Ivabradine selectively inhibits the pacemaker I_f current,



slowing the HR by approximately 10 beats/min and thereby reducing CV morbidity and mortality (56–58). In contrast, the long-term benefits of digoxin are mediated by facilitating overall improvement in cardiac function and are likely independent of baseline HR and not entirely explained by modest decreases in HR as a result of its vagomimetic effects. Thus, although digoxin and ivabradine have comparable long-term benefits, driven by a reduction in CV morbidity, their mechanisms of action are distinctly different, and they should not be viewed as mutually exclusive alternatives and may in fact be complementary in terms of clinical utility.

Collectively, the available evidence suggest that higher digoxin doses achieving SDCs thought to be therapeutic in the past (i.e., 1.0 to 2.0 ng/ml) do not result in added symptomatic, hemodynamic, or neurohormonal benefit and may have deleterious consequences on long-term survival, irrespective of sex. However, one of the major criticisms of the aforementioned studies is that higher SDC may simply be a surrogate for other high-risk measured or unmeasured clinical features not adjusted for in multivariate modeling. In this respect, prospective randomized clinical trial data would be invaluable.

Digoxin Use in Contemporary Clinical Databases

A number of retrospective studies of consecutive patients (59) and clinical trial databases (60) and prospective cohort studies (61) have questioned the efficacy and safety of digoxin therapy. Most notably, a study based on the AFFIRM (Atrial Fibrillation Follow-Up Investigation of

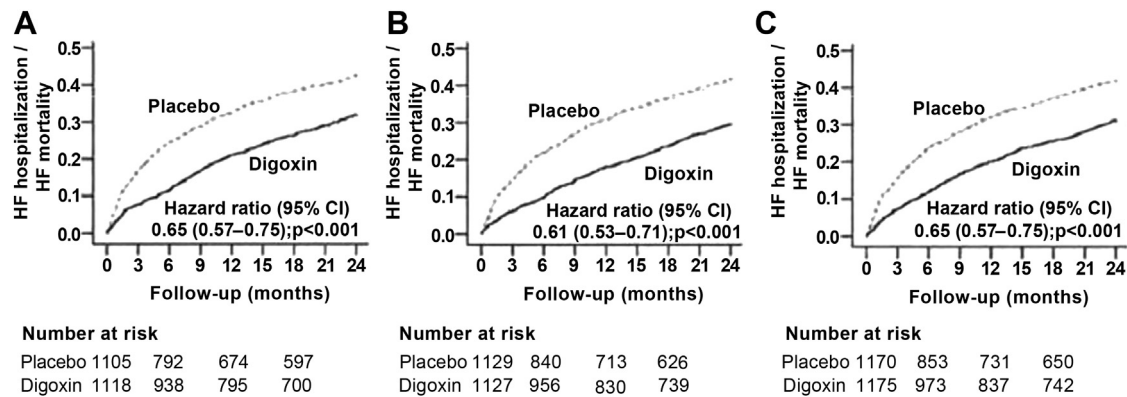


Figure 5 Kaplan-Meier Plots for Hospitalization or Death Due to HF by Treatment Groups in High-Risk Patients, Including NYHA Functional Class III or IV, LVEF <25%, and Cardiothoracic Ratio >55% in the DIG Trial

(A) NYHA functional class III or IV; (B) LVEF <25%; (C) cardiothoracic ratio >55%. Reprinted, with permission, from Gheorghiade et al. (50). CI = confidence interval; DIG = Digitalis Investigation Group; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

Rhythm Management) trial found digoxin therapy to be associated with an increased risk for mortality in patients independent of the presence or absence of HF (62). However, the results of this post-hoc analysis of the AFFIRM trial were challenged by a subsequent study using propensity-matched cohorts that found no evidence of increased mortality or hospitalization in patients taking digoxin at baseline (63).

It should be noted that these studies were non-randomized and subject to selection bias, because digoxin is

generally prescribed to patients with symptomatic HF despite optimal medical management. Even with sophisticated statistical techniques, it may be challenging to fully adjust for disease severity comprehensively and the indication for treatment by the provider. Furthermore, these post-hoc analyses were all based on prevalent digoxin use, and substantial differences in clinical characteristics may develop in the time frame between initial prescription and study enrollment. Thus, although existing and future administrative and clinical trial databases may provide useful

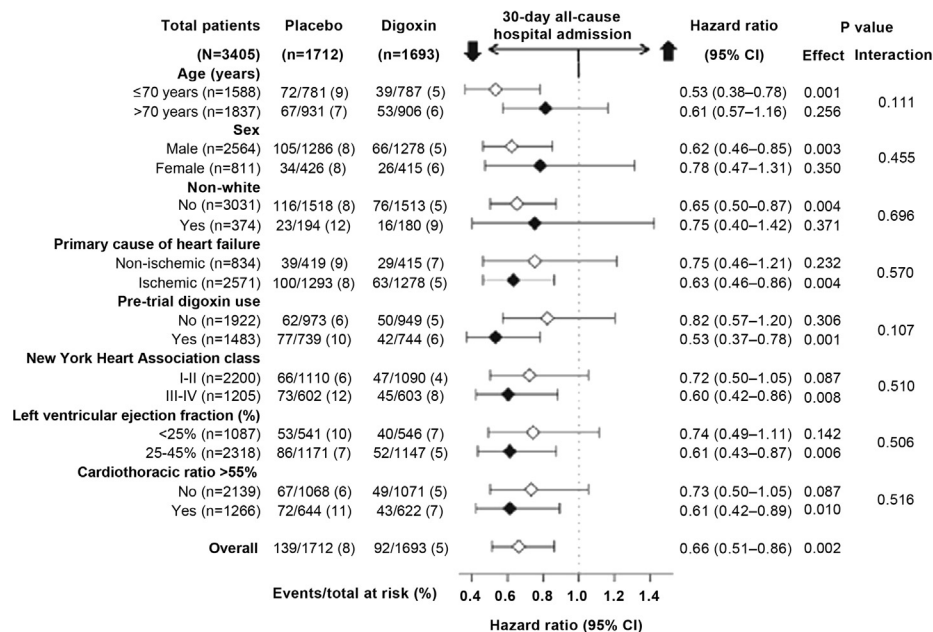


Figure 6 Effects of Digoxin on 30-Day Admissions in Subgroups of Older Patients in the DIG Trial

Reprinted, with permission, from Bourge et al. (51). CI = confidence interval; DIG = Digitalis Investigation Group.

information including, but not limited to, the epidemiology and natural history of HF, conclusions regarding the efficacy and safety of specific treatments should be interpreted with caution (64,65).

Future Research on Digoxin

Despite the success achieved in the management of HF with reduced EF in the ambulatory setting, patients with worsening chronic HF, defined as deteriorating signs and symptoms on standard therapy often leading to unscheduled clinic or emergency department visits or hospitalizations, experience unacceptable rates of CV morbidity and mortality. Digoxin is known to reduce all-cause and HF-specific hospitalizations and at lower SDCs (i.e., 0.5 to 0.9 ng/ml) and in certain high-risk groups (i.e., patients with NYHA functional class III or IV symptoms, left ventricular EFs <25%, and cardiothoracic ratios >55%) may improve survival. Despite safety concerns regarding supratherapeutic levels and fatal arrhythmias, the absolute incidence of digoxin toxicity requiring hospitalization is low both in the controlled setting of a study (6) and in the context of routine clinical practice (66,67). Thus, these data support a therapeutic trial of digoxin in patients experiencing worsening chronic HF despite standard therapy.

Additionally, the unique pharmacologic properties of digoxin provide a strong rationale to reevaluate its efficacy and safety in stable ambulatory patients with HF. It is the only inotrope known to increase cardiac output and reduce pulmonary capillary wedge pressure without increasing HR or decreasing blood pressure. In contrast, despite favorable hemodynamic actions, alternative oral inotropes have been associated with higher morbidity and mortality, particularly in the subset of patients with the worst symptoms (68,69). Thus, it is notable that digoxin therapy does not have long-term deleterious consequences, and its hemodynamic effects are not attenuated by chronic administration (i.e., Na^+/K^+ -adenosine triphosphatase is not up-regulated) (54-57). In addition, digoxin may have synergistic effects with β -blockers as an adjunct for reducing HR and mineralocorticoid receptor antagonists for its putative antifibrotic properties (32). Finally, digoxin therapy does not decrease blood pressure or worsen renal function, side effects that have traditionally limited the initiation and titration of several other evidence-based medications and diuretic agents.

It should be noted that the outpatients enrolled in the DIG trial differ markedly from an unselected contemporary HF population in terms of demographics (i.e., age, sex, and ethnicity) and background therapy. Thus, an appropriately designed and powered randomized, double-blind, placebo-controlled trial should be conducted to establish the broader clinical utility of digoxin in stable ambulatory patients with HF. All study participants should be taking β -blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and mineralocorticoid receptor antagonists or have documented intolerance or contraindications.

Prespecified subgroups should include women and elderly patients. Further trials might include patients with HF with preserved EF in whom the absolute benefit of digoxin appeared to be comparable at 2 years, a prespecified analysis, but not significant at study end, perhaps because of the smaller sample size and higher proportion of patients lost to follow-up (42). Similarly, additional research should be conducted in the 30% to 40% of patients with HF with comorbid atrial fibrillation in whom the combination of carvedilol and digoxin has been shown to improve rate control, left ventricular EF, and symptomatology compared with either agent alone (70).

The initial maintenance dose of digoxin in future studies should be based on an algorithm taking into account age, sex, ideal body weight, and renal function. However, a starting dose of 0.125 mg/day would be appropriate for most patients, with a smaller number of patients requiring a dose of 0.0625 or 0.250 mg/day. Clinician-investigators should be trained to distinguish between digoxin effect (i.e., scooped ST-segments), excess (i.e., second-degree atrioventricular block), intoxication (i.e., ventricular arrhythmias), and overdose (i.e., ventricular arrhythmias and hyperkalemia). A key question is whether serial SDCs are required for dose titration and to monitor for safety. In the DIG trial, although there were more patients in the digoxin arm with suspected clinical toxicity (11.9% vs. 7.9%), the proportion of patients requiring hospitalization for digoxin toxicity was low (2.0% vs. 0.9%) over a period of 3.5 years. Furthermore, outside of the context of a clinical trial, the incidence of digoxin toxicity has been estimated to be as low as 1% to 5% (66,67), and >95% of cases occur in patients with SDCs >2.0 ng/ml (71). Thus, with appropriate digoxin dosing, it may not be necessary to routinely measure SDCs in most patients to achieve a safe and efficacious level.

Although the gold standard for efficacy and safety will continue to be all-cause mortality, there is growing recognition that the “patient journey” may include impairments in day-to-day experience that are not fully captured by traditional outcome measures. Thus, validated patient-centered supplementary end points may be necessary to ascertain the net clinical benefit of existing and novel interventions. Given the renewed interest in reducing 30-day readmissions, hospitalization-free survival is a logical choice for long-term efficacy. Candidate endpoints for short-term clinical status might include the percentage of patients with worsening dyspnea, physician-assessed signs and symptoms, functional capacity, and quality of life. Finally, measuring echocardiographic parameters (filling pressures, chamber size, EF, and so on) and neurohormonal (norepinephrine, plasma renin activity, aldosterone, and so on) and biomarker levels (i.e., natriuretic peptide concentration) in at least a subset of patients might clarify the relative contribution of the hemodynamic and neurohormonal properties of digoxin on short-term and long-term morbidity and mortality in the current era of lower target SDCs and background therapy

with beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and mineralocorticoid receptor antagonists.

Conclusions

Patients with worsening chronic HF, defined as deteriorating signs and symptoms on standard therapy often leading to unscheduled clinic or emergency department visits or hospital admissions, experience clinical, hemodynamic, and neurohormonal deterioration despite recommended drug and device-based therapy. Digoxin is known to ameliorate signs and symptoms of HF, improve functional status, and reduce all-cause and HF-specific hospitalizations. Thus, a therapeutic trial of digoxin should be considered in patients with HF with reduced EF who remain symptomatic and at high-risk for admission despite medical management. Future research should be conducted to assess the efficacy and safety of digoxin in a more contemporary cohort of stable patients with HF, including those with preserved EFs and/or concomitant atrial fibrillation.

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